



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

ATTY.'S DOCKET: MAYUMI=1

In re Application of:)	Art Unit: 1632
)	
Tadanori MAYUMI et al)	Examiner: D. Nguyen
)	
Appln. No.: 10/070,252)	Washington, D.C.
)	
Nationalized: July 8, 2002)	Confirmation No. 9722
)	
I.A. No.: PCT/JP00/01267)	July 6, 2004 ¹
I.A. Date: March 4, 2000)	
)	
For: METHOD AND FORMULATION)	
FOR SUSTAINED RELEASE...)	

REPLY: REQUEST FOR RECONSIDERATION

Customer Window, Mail Stop
Honorable Commissioner for Patents
U.S. Patent and Trademark Office
2011 South Clark Place
Crystal Plaza Two, Lobby, Room 1B03
Arlington, Virginia 22202

Sir:

The present applicants acknowledge receipt of the Official Action mailed January 5, 2004, and they respectfully request favorable reconsideration and allowance.

Filed herewith is a petition for three months' extension of time and payment of the three months' late fee.

The claims in the present application remain as claims 1, 2, 4-6, 8, 9, 11 and 13. These claims define novel

¹ This Reply is timely filed with a petition for three months' extension of time and payment of three months' late fee, because Monday, July 5, 2004, was a legal holiday, i.e. the celebration of Independence Day which fell on Sunday, July 4, 2004.

and unobvious subject matter under Sections 102 and 103 for the reasons given below, and therefore these claims should be allowed. Accordingly, the applicants hereby respectfully request favorable reconsideration, withdrawal of the rejections and allowance of the present application.

Applicants wish to first review the background of the present invention and further provide a further explanation of the present invention in conjunction with the general state of the art.

It has long been desired to develop technology by which biologically active substances, especially those having a high molecular weight such as genes, antigenic proteins and physiologically active proteins, can be introduced into the cytoplasm in a desired and efficient manner without causing damage to the cell.

Nanospheres are vesicles which are typically made of polymeric matrices and which can encapsulate a large volume of drugs of high-molecular weight substances. However, administered alone, nanospheres are not easily taken up by the cells, and even when they are so taken up, the uptake is by endocytosis and the efficiency of introduction is very low because of lysis by a lysozyme during endocytosis process.

On the other hand, since liposomes can hold a number of substances and are still biocompatible, they have drawn the

attention of researchers as potential carriers for transporting physiologically active substances. However, with liposomes, the efficiency of introducing a desired substance into a cell is so low that the substance can hardly be introduced into the cytoplasm. To deal with this difficulty, various proposals have been made, including modifying the surface of liposomes with lectins, antibodies, etc. so that they become positively bound to cell surfaces. However, liposomes, whether surface-modified or not, are taken up by cells via endocytosis, so they are lysed by lysozyme and the proportion in which the substance of interest is actually transferred into the cytoplasm is at an extremely low level.

To overcome the above-mentioned problems, the present applicants have used fusogenic liposomes derived from Sendai virus as carriers for physiologically active substances, thereby successfully introducing the active substances into cells not by endocytosis, but by directly passing them through the cell membrane. But this alone is not sufficient.

Thus, if the fusogenic liposomes are used as carriers for physiologically active substances, the release of the physiologically active substances within the cells cannot be controlled, so the substance introduced into the cell is released all at one time, and its activity (or toxicity) is

not sustained. For example, in the case where a gene is introduced into the cytoplasm, the gene is decomposed in the cytoplasm and its expression is not sustained. In the case of a protein having a particular activity, such activity is not sustained and the protein has to be administered an increased number of times in a larger than desirable dose.

Thus, an object of the present invention is to introduce physiologically active substances into cells directly and efficiently and at the same time to control release of the substances within the cells, thereby efficiently exhibiting the intended physiological activity in the cell.

According to the present invention, the above-mentioned object has been attained by using a combination of nanospheres encapsulating the physiologically active substances with liposomes having fusogenic capability.

Please refer to Example 2, wherein release of a drug from FITC-dextran encapsulating poly(lactic acid) nanospheres was tested. As shown in Fig. 1, the FITC-dextran was desirably released in an amount of only about 6% even at day 4, and its slow release was evident. That is, the release profile of a drug within the cytoplasm could be controlled by appropriately changing the production conditions of nanospheres, and the nanospheres allowed the drug to be

released slowly in the cytoplasm. Also, Example 3 showed that the controlled release of a drug contained therein could be attained by changing the conditions of nanosphere preparation.

Please refer also to Example 4 and Fig. 4. The efficiency of gene expression is shown in samples of (a) the fusogenic liposomes (FL) encapsulating only a plasmic DNA containing nanospheres (nanospheres alone). As shown in Fig. 4, the group treated with the FL-DNA-nanospheres exhibited very high luciferase activity. The results indicate that the FL-DNA-nanospheres system, which is a combination of the fusogenic liposomes with nanospheres having sustained release of the DNA, is significantly useful to achieve efficient gene introduction into cells. The advantages of the combination are significant and unexpected for a person skilled in the art.

Claims 1, 2, 4-6, 8, 9, 11 and 13 have now been rejected under Section 102 as anticipated by both Fernandez and Dunn, both previously cited; or, alternatively, as obvious under Section 103 from these same citations, applied individually. These four (4) rejections are respectfully traversed.

First, neither Fernandez nor Dunn anticipates any of applicants' claims.

Fernandez discloses liposomes containing an active compound. However, Fernandez does not disclose a combination of fusogenic liposomes with nanospheres showing sustained release of the active compound. Accordingly, Fernandez does not disclose (and also does not teach or suggest) the efficient introduction of active compound into cells which is achieved by the present invention.

Dunn does not disclose a combination of nanospheres containing a physiologically active substance with a coating of liposomes having fusogenic ability derived from the Sendai virus. According to the combined features of the present invention, the active substance can be directly and efficiently introduced into cells without going through any endocytosis process. Moreover, applicants believe and submit that bio-adhesive adjuvants exemplified in Dunn are importantly different from a coat protein derived from the Sendai virus which provides the liposome with fusogenic properties. Thus, applicants believe and submit that Dunn does not disclose (and does not teach or suggest) the present invention.

The alternative rejections under Sections 102 and 103 based on Fernandez and Dunn individually appear to be in part based on the supposition that features in applicants' claims which are not expressly disclosed in Fernandez and Dunn

are nevertheless inherent in these citations. However, applicants wish to make clear for the record that inherency must be reasonably certain or inevitable, and there is no reasonable certainty, nor is it inevitable, that what is disclosed in Fernandez and Dunn meets or makes obvious the subject matter of applicants' claims.

Thus, as regards Section 102, attention is respectfully invited to *In re Brink*, 164 USPQ 247, 249, wherein the Court stated:

Absent a showing [by the PTO] of some reasonable certainty of inherency, the rejection ... under 35 U.S.C. 102 must fail.

Please also see *Ex parte Cyba*, 155 USPQ 756, 757 (1967); and *In re Oelrich*, 212 USPQ 323, 326 (1981).

The situation is similar with respect to rejections based on Section 103, as it is clear that the obviousness rejections are in part based on what is presumed to be inherent in the references, but which is actually not inherent. Moreover, in this regard, applicants believe that the examiner will agree that normally a rejection will be based on what a reference shows rather than what it does not show, i.e. a rejection normally is not to be based on silence in a reference, *In re Burt et al*, 148 USPQ 548, 553 (CCPA 1966) :

Silence in a reference is hardly a proper substitute for an adequate disclosure of facts from which a conclusion of obviousness may justifiably follow.

Attention is also respectfully invited to *In re Henderson*, 146 USPQ 372, 375 (CCPA 1965), and *In re Spormann et al*, 150 USPQ 449, 452 (CCPA 1966), both of which in part concerned rejections under Section 103 based in part on assumed inherency, which rejections were reversed. A more recent case in this regard is *In re Shetty*, 195 USPQ 753, 756 (CCPA 1977).

There is no reasonable certainty or inevitability that either Fernandez or Dunn discloses subject matter which either inherently anticipates applicants' claims, or any inherent subject matter upon which an obviousness rejection can be properly based.

Applicants respectfully request withdrawal of the rejections based on Fernandez and Dunn.

Claims 1, 2, 4-6, 8, 9, 11 and 13 have also been rejected under Section 103 as obvious from Fernandez or Dunn, either in view of Dzau USP 5,631,237 (Dzau), newly cited. These rejections are also respectfully traversed.

Fernandez and Dunn have been discussed above, where it is pointed out that these citations neither anticipate nor make obvious the subject matter of applicants' claims. The present rejection is predicated upon the assumption that Dzau

provide something missing from Fernandez and Dunn, and that it would have been obvious to the person of ordinary skill in the art to abstract such missing subject matter from Dzau and incorporate it into Fernandez and Dunn, and thereby obtain applicants' claimed subject matter.

Dzau discloses an application of the Sendai virus as a component of fusogenic liposomes in the delivery of a biologically active agent. However, Dzau does not disclose the combination of the liposomal carrier with nanospheres containing an active substance to prepare a slow-release composition for introducing the active substance into the cytoplasm.

With respect, applicants do not see that the person of ordinary skill in the art, absent having first reviewed applicants' specification which of course was not available to such person of ordinary skill in the art at the time the present invention was made, would have even attempted to combine Dzau with either Fernandez or Dunn, so as to modify either Fernandez or Dunn by abstracting by Dzau for use in changing something in Fernandez or Dunn. The citations are too diverse from one another, and it would not have been obvious to react a Sendai virus with encapsulated liposomes of Fernandez or Dunn. Certainly, the prior art provides no reasonable certainty of obtaining applicants' results.

Applicants' claims define non-obvious subject matter. Accordingly, applicants respectfully request withdrawal of the rejections based on Fernandez in view of Dzau and Dunn in view of Dzau.

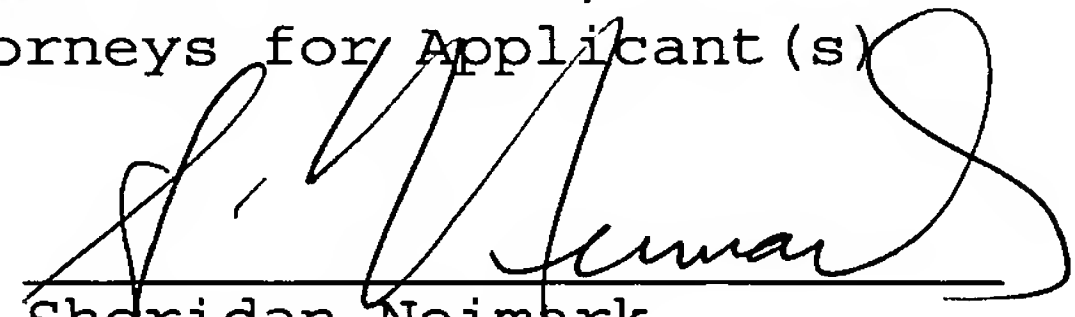
For the reasons stated above, applicants do not believe that a person skilled in the art would have been motivated to combine nanospheres with fusogenic liposomes without knowledge of the present invention. Thus, the invention of the present application is novel and unobvious over the cited prior art references.

Applicants respectfully request favorable reconsideration and allowance.

Respectfully submitted,

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